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Ectopic adrenocorticotropic hormone (ACTH) syndrome: two case reports.

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Abstract

BACKGROUND: Clinically, the incidence of ectopic adrenocorticotropic hormone (ACTH) syndrome (EAS) is often obscured, making it difficult to identify the primary lesion. This can pose challenges in both diagnosing and treating the disease. Therefore, this paper presents two cases of EAS to share insights and guide diagnosis and treatment approaches.

DESCRIPTION OF CASES: Case 1 is a male patient aged 71, and Case 2 is a female patient aged 61. EAS was considered for both patients according to the medical history and auxiliary examination results. After the blood glucose and blood potassium were slightly stable, Case 1 received the total right adrenalectomy and the left subtotal adrenalectomy. After the surgery, a positron emission tomography-computed tomography (PET-CT) was used to identify the primary lesion in Case 1, and the result showed primary neuroendocrine tumors originating from the thymus with metastasis. A chest CT scan with contrast for Case 2 confirmed the presence of multiple soft tissue nodules in both lungs, suspected of being tumor lesions, along with mediastinal lymph node enlargement. A CT-guided lung puncture was not performed due to a progressive decrease in platelets, and the patient died due to severe lung infection eventually.

CONCLUSIONS: PET-CT can be an effective method for diagnosing EAS. Early control of hypercortisolism is vital in preventing life-threatening infections in EAS patients.

Abbreviations:

ACTH	- adrenocorticotropic hormone
EAS	- Ectopic ACTH syndrome
P	- pulse
BP	- blood pressure
WBC	- white blood cell
FT 3	- free triiodothyronine
FT 4	- free thyroxine
TSH	- thyroid stimulating hormone
PET-CT	- positron emission tomography-computed tomography
CT	- computed tomography
MRI	- Magnetic resonance imaging
IHC	- immunohistochemistry
MyoD1	- myogenic differentiation 1
NSE	- neuron specific enolase
EMA	- epithelial membrane antigens
CgA	- chromogranin A
Syn	- synapsin
NF	- neurofibromatosis
CD34	- cluster of differentiation 34
PO	- peros
QID	- quarterindie
SpO_2	- Oxygen saturation

CASE REPORT

INTRODUCTION

Ectopic adrenocorticotropic hormone (ACTH) syndrome (EAS) is a rare disease that accounts for 10-20% of ACTH-dependent Cushing syndrome (Ilias *et al.* 2005; Isidori *et al.* 2006). EAS is associated with excess mortality due to severe symptoms, including edema, hypokalemia, hypertension, hyperglycemia, osteoporosis and so on (Ilias *et al.* 2005). The disease is mainly caused by different ectopic tumors that secrete excessive ACTH or its analogs, which stimulate adrenal cortical hyperplasia and excessive glucocorticoid secretion (Lacroix *et al.* 2015). Diagnosis and treatment of EAS mainly rely on a combination of clinical assessment, biochemical tests, multimodal imaging, and other tests. However, in many EAS patients, the primary lesion may be too small and difficult to detect, making the disease's diagnosis and treatment challenging (Hayes and Grossman, 2018). This report presents two EAS cases and focuses on their clinical features, examination, diagnosis, and management, which is expected to broaden the vision and improve understanding of the disease for clinicians. The study protocol was approved by the ethics committee of Panzhihua Central Hospital, and informed consent was obtained from each patient.

CASE PRESENTATION

Case 1

A 71-year-old male patient was admitted to the hospital on September 16, 2019, due to progressive edema and weakness in both lower limbs for more than two months. He also experienced redness, swelling, and pain in the rear of his left leg for more than one day. After admission, the diagnosis was cellulitis on the left leg. With anti-inflammatory treatment, the patient's condition improved. The patient was diagnosed with type 2 diabetes, hypertension, and hyperlipidemia more than eight years ago, but his blood glucose, blood pressure, and blood lipid levels were poorly controlled. Additionally, he received treatment for stomach bleeding over six years ago, but the treatment details are unknown. Five years ago, he was diagnosed with lumbar disc herniation at a local hospital and received medical treatment. However, due to poor treatment, he continues to experience repeated low back pain.

At the time of hospitalization, his body temperature and pulse were normal, and his blood pressure (BP) was 143/88 mmHg. Physical examination revealed redness and swelling of the skin on the posterior medial part of his left leg, with increased skin temperature and obvious tenderness. The results of the blood routine examination showed an increase in the white blood cell (WBC) count, granulocyte ratio, and neutrophil count, while the platelet count decreased. The blood gas analysis revealed a decrease in potassium ions and an increase in pH, while the sodium ion level was normal. The 24-hour urine potassium level was 128.64 mmol/D (blood potassium level of 3.30 mmol/L on the same day). The sex hormone results indicated a decrease in testosterone levels, while follicle-stimulating hormone, luteinizing hormone, pituitary prolactin, estradiol, and progesterone levels were normal. The thyroid function results showed a decrease in the levels of triiodothyronine, thyroid stimulating hormone, free triiodothyronine (FT 3), and free thyroxine (FT 4), while the hypersensitive thyroid stimulating hormone (TSH) level was normal (refer to Table 1). The results of the endocrine examination indicated that levels of Renin-angiotensin aldosterone, catecholamine, 11-deoxycorticosterone, and aldosterone were normal in the supine position, while cortisol rhythm was absent (as shown in Table 1). All dexamethasone inhibition tests yielded negative results. The results of the computed tomography (CT) examination of both kidneys and adrenal glands showed the following: 1. The edges of both kidneys were blurred, with a few cord-like exudation shadows around the kidneys, and there were patchy calcified plaques in bilateral renal arteries. 2. Bilateral adrenal glands were slightly thickened, and their margins were blurred. The magnetic resonance imaging (MRI) of the pituitary gland was normal. During the contrast-enhanced cardiothoracic CT, the following were noted: 1. The thin-walled cavity in the left upper lobe of the lung was considered multiple benign lesions. 2. Interstitial fibrosis was observed in the subpleural area of both lungs. 3. Multiple enlarged lymph nodes were noted in the mediastinum. 4. There was a small thickening of the left lower pleura. The whole-body bone imaging revealed abnormal radioactive uptake at the right shoulder joint and the right iliac bone near the sacroiliac joint, which may be caused by benign lesions. A bone marrow puncture revealed megakaryocyte maturation disorder. Color Doppler ultrasound showed bilateral neck and left subclavian lymph node enlargement. Lymph node resection and biopsy were performed, and the immunohistochemistry (IHC) showed: Tumor cells TFE3 (-), myogenic differentiation 1 (MyoD1) (-), desmin (-), myogenin (-), S-100 (-), neuron specific enolase (NSE) (+), AE1 / AE3 (+), vimentin (-), epithelial membrane antigens (EMA) (+), chromogranin A (CgA) (-) (Figure 1A), synapsin (Syn) (+) (Figure 1B), neurofibromatosis (NF) (-), cluster of differentiation 34 (CD34) (-), reticulocyte staining (nests), calponin (-), Ki-67 (+ about 10%). Therefore, the results of immunohistochemical staining supported the diagnosis of metastatic neuroendocrine carcinoma.

Based on the patient's symptoms and relevant clinical examinations, EAS was considered, but the patient's primary lesion could not be precisely identified. Meanwhile, the patient's general condition deteriorated progressively during hospitalization. Mitotane, a drug that can be used to treat hypercortisolemia, is not easily accessible in our hospital. The therapeutic effects of available drugs for hypercortisolemia, such as cyproheptadine and mifepristone, were not potent.

Tab. 1. Laboratory examination results of case1 and case 2

Variable	Case 1	Case 2	Reference Interval
Blood routine			
White blood cell (/L)	15.7×10^9	12.69×10^9	$4.0\text{-}10.0\times10^9$
Granulocyte ratio (%)	88.3	91.3	50-70
Neutrophil count (/L)	13.87×10^9	12.5×10^9	$1.80\text{-}6.30\times10^9$
Platelet (/L)	98×10^9	$60x10^9$	$100\text{-}300\times10^9$
Blood gas analysis			
PH	7.536	7.515	7.35-7.45
Sodium ion (mmol/L)	136.9	137.2	135-155
Potassium ion (mmol/L)	1.94	2.48	3.5-5.5
Blood potassium (mmol/L)	2.27-3.26	2.53-3.37	3.5-5.5
24-hour urine potassium (mmol/24h)	128.64	93.73	25-125
Blood potassium on the same day (mmol/L)	3.3	2.53	3.5-5.5
Sex hormone			
Testosterone T (ng/dL)	77.21	106.02	0-45.62
Follicle-stimulating hormone (miu/ml)	67.3	1.57	23.0-116.3
Luteinizing hormone (miu/ml)	34.5	0.01	15.6-54
Pituitary prolactin (ng/ml)	11.3	7.93	1.8-20.3
Estradiol (pg/ml)	22.4	32.9	0-32.2
Progesterone (ng/ml)	3.2	3.5	0-0.73
Thyroid function			
Triiodothyronine (nmol/L)	0.61	1.21	0.92-2.79
Thyroid stimulating hormone (nmol/L)	51.41	53.6	58.1-140.6
Free triiodothyronine (FT 3, pmol/L)	2.04	2.86	3.5-6.5
Free thyroxine (FT 4, pmol/L)	8.81	8.82	11.5-23.0
Hypersensitive thyroid stimulating hormone (mIU/L)	1.795	0.104	0.55-4.78
Cortisol rhythm (ng/ml)			
8:00 am	524.3	>500	-
4:00 pm	507.6	>500	-
12:00 am	514.2	>500	-
ACTH (pg/ml)	67.81	349.1	7.2-63.3

PH: Pondus Hydrogenii; ACTH: adreno-cortico-tropic-hormone.

Therefore, it is challenging to correct hypercortisolemia quickly with the available drugs.

Unilateral adrenalectomy should be considered to relieve hypercortisolemia and improve the patent's general conditions. After the general conditions were improved, the other side's subtotal resection could be performed, followed by the CT scan to determine whether there was a malignant tumor in the patient. During the treatment, insulin dosage was increased, and the large daily dose of potassium supplement with spironolactone 80 mg PO (peros) QID (quarterindie) was also given to the patient. After the blood glucose and blood potassium were slightly stable, the patient was immediately transferred to the department of urology for the total right adrenalectomy (October 21st, 2019) and the left subtotal adrenalectomy (October 28th, 2019). The patient's postoperative condition indicated that cortisol levels decreased rapidly after the operation, with the lowest reading of 3.26 μg/dL at 8 a.m. Prednisone 10 mg PO QD was given to supplement glucocorticoids. In addition, the patient exhibited high blood pressure (the blood pressure increased to a maximum of 144/92 mmHg) and received treatment to control hypertension. All antihypertensive medication was discontinued on the fifth day post-surgery. The patient's blood potassium levels occasionally decreased post-surgery, but supplementation with potassium chloride normalized levels. By Day 9 after

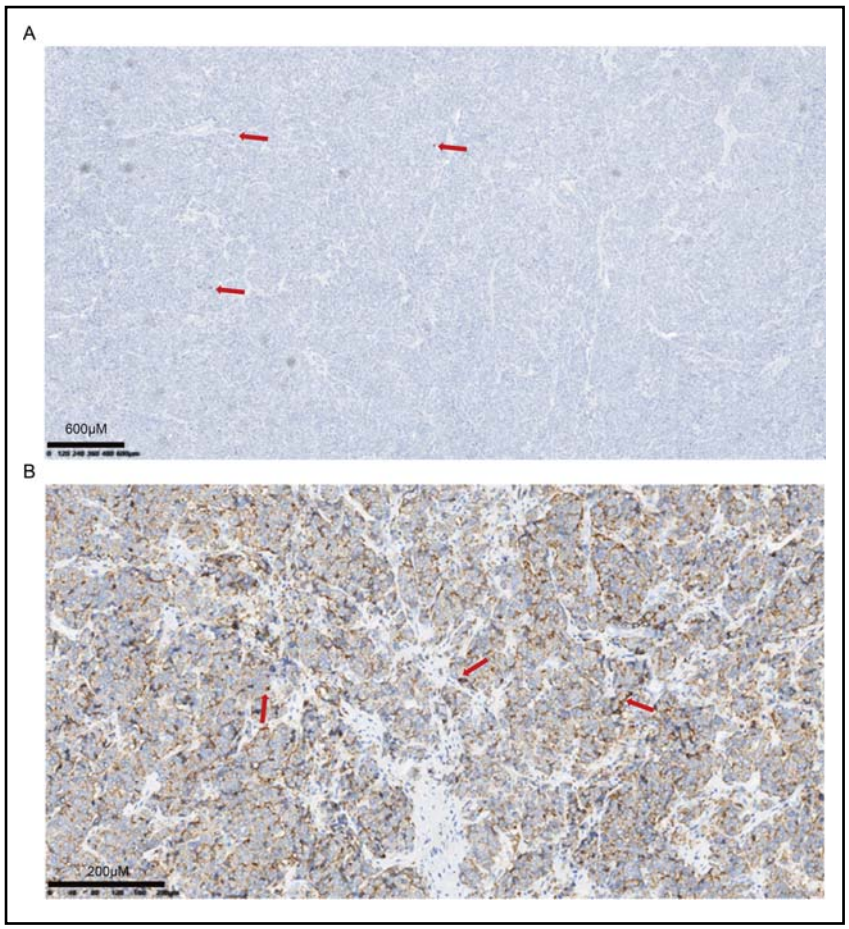

Fig. 1. The expression of CgA and Syn in metastatic neuroendocrine carcinoma detected by IHC. (A) The CgA (+) expression of in metastatic neuroendocrine carcinoma. (B) The Syn (+) expression of in metastatic neuroendocrine carcinoma. The red arrow points to IHC-positive cells. IHC: immunohistochemistry; CgA: chromogranin A; Syn: synapsin.

the operation, serum potassium was normal without any potassium supplementation. Blood sugar levels remained high following the procedure, and Ganshulin (30 R) was administered daily to control blood sugar. Insulin was discontinued on Day 11 post-surgery, and metformin and acarbose were administered to control blood glucose, which was well-managed (the highest level recorded was 11.4 mmol/L). The patient's platelet counts were normal upon admission. However, on the day of the operation, platelets dropped to 70×10^9/L and then to 42×10^9/L. Post-surgery, 10U of platelets were infused, and levels increased to 74×10^9/L. Platelets increased progressively and returned to normal levels by the seventh day post-surgery. On November 6, 2019, the patient's overall condition improved, and a whole-body PET-CT scan was performed (see Figure 2). The results revealed several abnormalities: 1) Increased glucose metabolism was observed in anterior and superior mediastinal masses, which were likely primary neuroendocrine tumors originating from the thymus. 2) Abnormal glucose metabolism was detected in the upper part of the sternum, cervical, thoracic, and lumbar vertebrae, suggesting tumor metastasis. 3) Abnormal glucose metabolism was also found in the left and right cervical lymph nodes and bilateral supraclavicular lymph nodes. Due to the tumor's metastasis and the patient's current condition and preferences, primary tumor resection was not recommended. Currently, the patient enjoys a good quality of life and is still undergoing follow-up.

Case 2

A 61-year-old female was admitted to the hospital for repeated facial edema lasting for more than 11 years, as well as general fatigue and edema for the past ten days. No significant medical history was found in her past. At the time of admission, the patient's blood pressure was recorded as 140/88 mmHg with a 98% oxygen saturation (SpO_2). During examination, the patient exhibited characteristic facial features of chronic illnesses, including visible vellus hair on the upper lip, facial and eyelid edema. However, her heart, lung, and abdomen functions were normal, and there was no joint swelling except for mild edema on both lower limbs. Blood routine examination showed an increase in WBC and granulocyte ratio, as well as a decrease in platelets. Blood gas analysis indicated a decrease in the level of potassium ion, while pH and sodium ion levels were normal. Thyroid function analysis showed a decrease in FT3, FT4, TSH, and thyroid stimulating hormone, whereas triiodothyronine was normal. Additionally, 24-hour urine potassium was measured at 93.73 mmol/D (with a blood potassium level of 2.53 mmol/L on the same day). Sex hormone

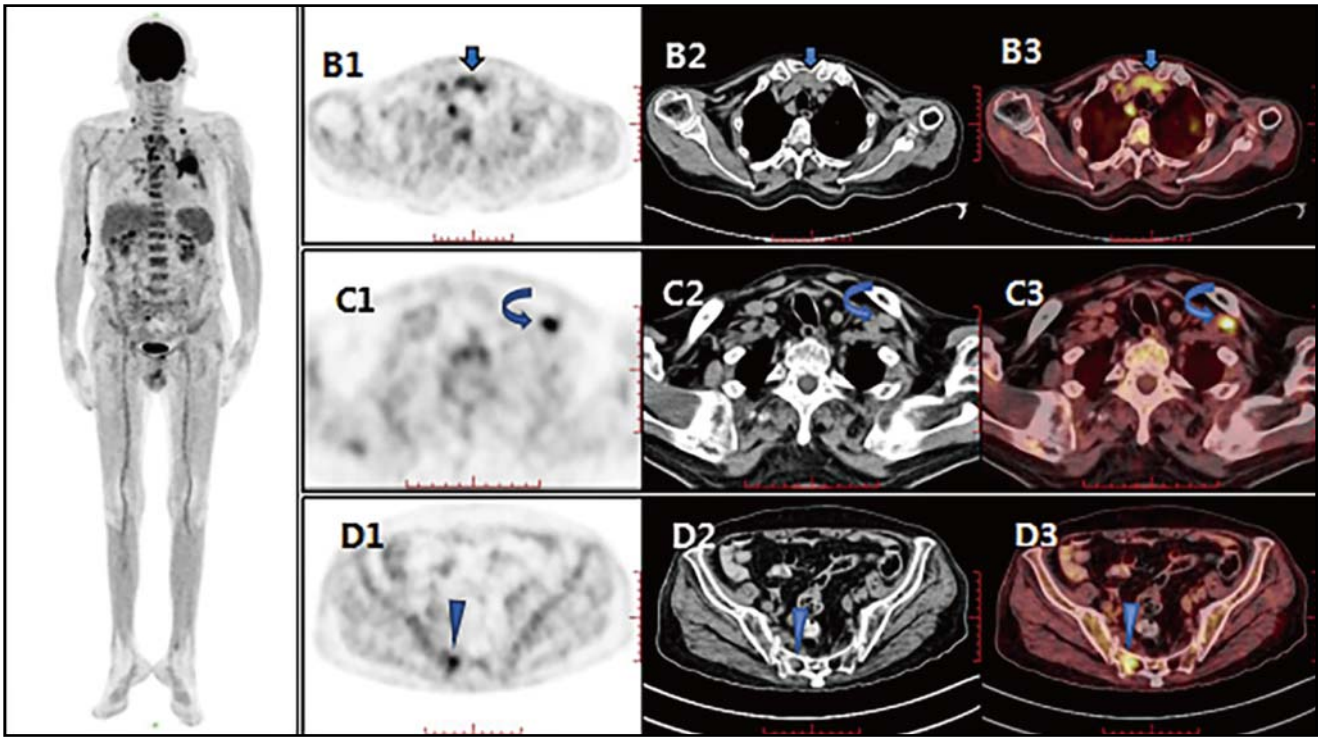

Fig. 2. The results of PET-CT. B1-B3 showed the thymic tumor; C1-C3 showed the left supraclavicular lymph node metastasis; D1-D3 showed the sacral metastasis involving the right second sacral foramen. PET-CT: positron emission tomography-computed tomography.

assessment revealed an increase in testosterone T, estradiol, and progesterone, and a decrease in follicle-stimulating hormone and luteinizing hormone, while the level of pituitary prolactin was normal. Endocrine testing showed cortisol levels to be higher than 500 ng/mL when measured at 8:00 a.m. 4:00 p.m. and 12:00 midnight (Table 1). Dexamethasone tests with large and small doses resulted in negative findings. A pituitary MR scan and enhancement revealed no significant abnormalities, while a renal and adrenal CT scan and enhancement showed bilateral adrenal thickening of about 2.0cm, with nodular changes in the left adrenal part, indicating adrenal cortical hyperplasia. A chest CT scan with contrast confirmed the presence of multiple soft tissue nodules in both lungs, suspected of being tumor lesions, along with mediastinal lymph node enlargement and a slight effusion in the right chest. The bilateral adrenal glands were also found to be thickened and hypertrophic (Figure 3).

Based on the patient's medical history and auxiliary examination results, a diagnosis of lung cancer and ectopic ACTH syndrome was considered. A CT-guided lung puncture was planned, but due to a progressive decrease in platelets (with the lowest value at 12×10^9/L), the puncture could not be performed during the treatment process. On the 17th day of admission, the patient developed a high fever and gradually experienced chest tightness, dyspnea, and hemoptysis. On the 20th day of admission, the patient left the hospital, and two days after being discharged, the patient died in a local hospital.

DISCUSSION

EAS is an extremely rare condition in clinical practice (Ilias *et al.* 2005; Isidori *et al.* 2006). As EAS has severe symptoms caused by hypercortisolemia and tumor tissues, it leads to a significant increase in mortality compared with the general Cushing's syndrome (Ilias *et al.* 2005). In the past, lung cancer was considered the only source of ACTH secretion, but with years of investigation, various tumors, including thymic cancer, pancreatic cancer, medullary thyroid carcinoma, and pheochromocytoma, have been found to secrete ACTH (Isidori *et al.* 2006; Isidori and Lenzi, 2007; Sun *et al.* 2012; Witek *et al.* 2015; Castro Oliveira *et al.* 2019; Krylov *et al.* 2020; Shayesteh *et al.* 2020). This makes it more challenging to diagnose and locate the primary disease causing EAS. Although our two cases did not present with typical signs of Cushing's syndrome, such as a "moon face", "buffalo hump", or polyhemoplasmia, they exhibited severe and uncontrollable symptoms, including alkalemia, hypokalemia, diabetes, hypertension, and edema. Additionally, the diagnosis of EAS was supported by biochemical examination results, endocrine tests, imaging, and pathological analysis.

In the diagnosis and treatment of these two cases, we found both similarities and differences in clinical symptoms and related tests. These findings underscore the importance of deepening our understanding of this disease. From a platelet perspective, both cases had thrombocytopenia, but only limited reports show that ectopic ACTH is related to hematological changes. The

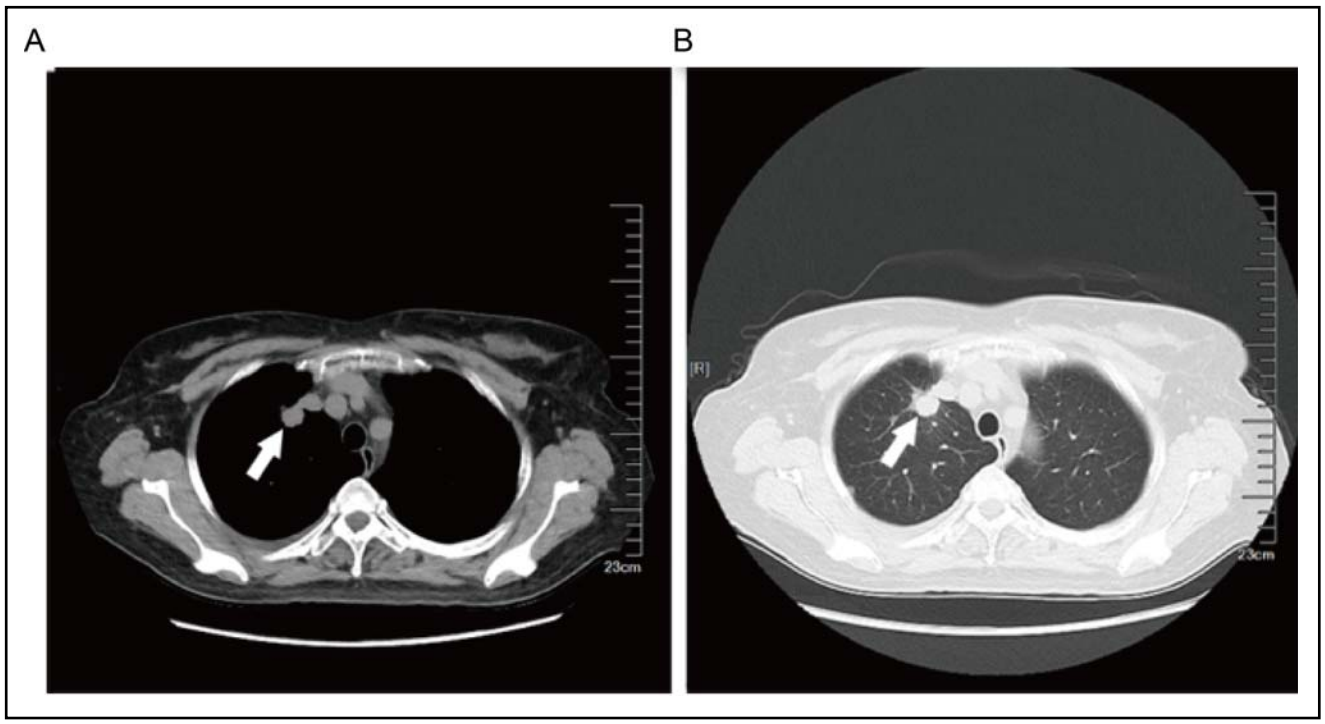

Fig. 3. The results of lung CT. A. Lung CT mediastinal window, the arrow showed the location of the tumor. B. Lung CT lung window. The arrows showed the location of the tumor. CT: computed tomography.

first case report suggesting a link between platelets and the primary tumor was published by L. Gullo *et al.* in 1992 (Gullo *et al.* 1992), who proposed that the tumor secretes serum factors that inhibit hematopoietic function and cause thrombocytopenia (Aabo *et al.* 1983; Mandaliya *et al.* 2014). However, in Case 1, platelet levels returned to normal only after hypercortisolemia was relieved, which contradicts Gullo's views. Therefore, further research is needed to determine whether cortisol inhibition is the cause of thrombocytopenia. Both cases showed secondary hypothyroidism at the initial detection stage, as noted in previous studies (Hu *et al.* 2014; Jin *et al.* 2019), but thyroid function returned to normal after adrenal gland removal. Secondary hypothyroidism may be caused by high-dose cortisol secreted by adrenal glands that inhibit pituitary TSH. In terms of androgen changes, which have not been well-studied in EAS cases, we observed decreased testosterone in Case 1 and elevated testosterone and signs of masculinization in Case 2. We speculate that these differences may be related to the severity of the disease, with the malignant degree of Case 2 being higher and adrenal cortex hyperplasia being more serious, leading to increased androgen secretion.

The above-mentioned analyses have represented our observations and examinations during the patients' hospitalization. These observations can provide inspiration to clinicians and advance studies on EAS. Based on our accumulated understanding during the treatment, it is important to pay more attention to changes in blood hormones and platelets caused by clinical work disease. Immediate measures should be taken if a decline in platelets is detected. Prioritizing the removal of the primary lesion is preferable. If this is not possible, the resection of both adrenal glands is a good alternative. In Case 1, PET-CT was necessary to determine the primary lesion. Therefore, if finding the primary lesion proves difficult in clinical practice, PET-CT can be used as an effective method. Case 2's death was attributed to severe pulmonary infection, which is consistent with previous reports (Sathyakumar *et al.* 2017), suggesting that early control of hypercortisolism is vital in preventing life-threatening infections associated with the disease.

ACKNOWLEDGMENTS

We would like to express our special thanks to Professor Xianling Wang in Beijing 301 Hospital for the treatment of Case 1 presented in the study.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest

The authors declare that they have no conflict of interest.

Ethical Approval

The study protocol was approved by the ethics committee of Panzhihua Central Hospital.

Informed Consent

Informed consent was obtained from each patient.

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